

Attorney's Docket No.: 12071-011002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Lee A. Mizzen *et al.* Art Unit : 1631
Serial No. : 08/977,787 Examiner : Mary Zeman
Filed : November 25, 1997
Title : IMMUNE RESPONSES USING COMPOSITIONS CONTAINING STRESS
 PROTEINS

Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF DR. LEE MIZZEN

I, Lee Mizzen, do hereby declare that:

1. I am a co-inventor of the subject matter described and claimed in the patent application referenced above.
2. I am also the Vice-President for Scientific Affairs for Stressgen Biotechnologies Corporation. In that capacity, I have become familiar with the clinical studies that were conducted with a fusion protein that contains a stress protein and a human papilloma virus (HPV) antigen. Details regarding the design of those studies, the results obtained, and their significance, follows.
3. Patients who had persistent anal high-grade squamous intraepithelial lesions (HSIL) were studied. Anogenital warts were not a trial parameter, but a retrospective review of the medical records of the first 22 patients enrolled at one site was undertaken to estimate the quality and frequency of responses of anogenital warts. The patients were typed for HPV by PCR assay using cells obtained from an anal swab, but the patients were not required to score positive for HPV type 16 (HPV16) to be enrolled in the study.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

February 23, 2002
Date of Deposit

Lee A. Mizzen
Signature

Lee A. Mizzen
Typed or Printed Name of Person Signing Certificate

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4. Patients received three subcutaneous injections of either 100 µg of HspE7 or placebo at monthly intervals. They were assessed for treatment response by anal Pap smears, high-resolution anoscopy (HRA) with biopsy, and global physician assessment. Non-responders (*i.e.*, patients with persistent anal HSIL) after 12 or 24 weeks in the controlled trial were allowed to crossover to an open-label trial where they received three injections of 500 µg of HspE7 at monthly intervals.

5. At the time of their entry into the open-label trial, 14 of the 22 patients (64%) had persistent anogenital warts. One month after the final treatment with 500 µg of HspE7, two patients (14%) had no detectable warts, 11 patients (79%) had a reduction in the size or number of warts (relative to the size or number at the beginning of the open-label trial), and one patient (7%) experienced an increase in wart size. Four months after the final dose of HspE7, one additional patient experienced an improvement from partial to complete response (characterized as having no visible warts), giving a total of three (21%) complete responders. None of these responders experienced a relapse during the six-month evaluation period.

6. In all 14 patients diagnosed with anogenital warts, DNA of multiple HPV types was detected in anal swab specimens. Most patients whose warts improved (85%) were not HPV16 positive. HPV types 6 and/or 11 were frequently detected. These data suggest that patients infected with HPV other than type 16 can respond to HspE7 treatment, and that anogenital warts, which are commonly associated with HPV types 6 and 11, can be treated by HspE7. This is surprising and beneficial. Many patients are infected with multiple types of HPV, indicating that infection with one HPV type does not provide protection against subsequent infection with a second HPV type. Thus, one would not have expected administration of an immunotherapeutic agent containing an antigen from a single HPV type (here, the E7 protein of HPV16) would benefit patients infected with other HPV types (*i.e.*, non-HPV16). One of the benefits of this unexpected result is that Applicants' immunotherapeutic agent (HspE7) can be used to treat diseases caused by different HPV types (here, anal HSIL and anogenital warts). Therefore, it may not be necessary to develop separate therapies for each HPV type as was previously

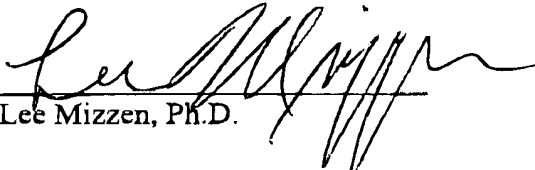
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thought. Accordingly, with a single therapeutic agent, HspE7, a greater number of patients with different manifestations of HPV infection (*e.g.* dysplasia and warts) can be treated.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. These statements were made with the knowledge that making willfully false statements and the like is punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such statements may jeopardize the validity of any patent issuing from the present application.

Feb. 28, 2002
Date


Lee Mizzen, Ph.D.